Comparison between two bone substitutes for alveolar ridge preservation after tooth extraction: Cone-beam computed tomography results of a non-inferiority randomized controlled trial

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Abstract: AIM To test the non-inferiority of demineralized bovine bone mineral (DBBM) compared to DBBM with 10% collagen (DBBM-C) for maintenance of bone volume after tooth extraction in the anterior maxilla. MATERIALS AND METHODS Sixty-six patients were randomly treated with DBBM or DBBM-C, both of which were covered with a collagen matrix for ridge preservation in the anterior maxilla. Cone-beam computed tomographic analysis was performed immediately and 4 months after treatment. The primary outcome, for which non-inferiority of DBBM was tested, was change in the horizontal ridge width 1 mm below the buccal alveolar crest (HW-1) 4 months after extraction. RESULTS Four months after extraction, HW-1 measured -1.60 mm ± 0.82 mm for DBBM-C, while the DBBM group showed a mean loss of -1.37 mm ± 0.84 mm (p = 0.28, 0.23 [95% CI: -0.19; 0.64]). The horizontal ridge width at 3 mm (HW-3) showed -0.98 mm (±0.67 mm) for DBBM-C and -0.84 mm (±0.62 mm) for DBBM (p = 0.40, 0.12 [95% CI: -0.19; 0.45]), and the horizontal ridge width at 5 mm (HW-5) showed -0.67 mm (±0.47 mm) for DBBM-C and -0.56 mm (±0.48 mm) for DBBM (p = 0.36, 0.11 [95% CI: -0.13; 0.34]). CONCLUSIONS The present clinical trial demonstrated non-inferiority of DBBM compared to DBBM-C for maintenance of alveolar bone volume 4 months after tooth extraction in the anterior maxilla.

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Comparison between two bone substitutes for alveolar ridge preservation after tooth extraction: Cone beam computed tomography results of a non-inferiority randomized controlled trial

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Running title: CBCT comparison between two bone substitutes in anterior post-extraction sockets.

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Abstract

Aim: To test the non-inferiority of demineralized bovine bone mineral (DBBM) compared to DBBM with 10% collagen (DBBM-C) for maintenance of bone volume after tooth extraction in the anterior maxilla.

Materials and Methods: Sixty-six patients were randomly treated with DBBM or DBBM-C, both of which were covered with a collagen matrix for ridge preservation in the anterior maxilla. Cone beam computed tomographic analysis was performed immediately and 4 months after treatment. The primary outcome, for which non-inferiority of DBBM was tested, was change of the horizontal ridge width 1 mm below the buccal alveolar crest (HW-1) 4 months after extraction.

Results: Four months after extraction, HW-1 measured -1.60 mm±0.82 mm for DBBM-C, while the DBBM group showed a mean loss of -1.37 mm±0.84 mm (p=0.28, 0.23 [95% CI -0.19;0.64]). The horizontal ridge width at 3 mm (HW-3)

showed -0.98 mm (±0.67 mm) for DBBM-C and -0.84 mm (±0.62 mm) for DBBM (p=0.40, 0.12 [95% CI -0.19; 0.45]), and the horizontal ridge width at 5 mm (HW-5) showed -0.67 mm (±0.47 mm) for DBBM-C and -0.56 mm (±0.48 mm) for DBBM (p=0.36, 0.11 [95% CI -0.13;0.34]).

Conclusions: The present clinical trial demonstrated non-inferiority of DBBM compared to DBBM-C for maintenance of alveolar bone volume 4 months after tooth extraction in the anterior maxilla.

Clinical Relevance

Scientific rationale for study: Spontaneous healing, after extraction, mostly leads to inadequate sites for implant therapy. Ridge preservation decreases such an effect. However, there is a lack of evidence comparing different biomaterials in terms of clinical outcomes and cost effectiveness ratio.

Principal findings: DBBM can be as effective as DBBM-C for alveolar ridge preservation in the anterior region of the maxilla (canines to canines).

Practical implications: Defects with less than 50% of buccal bone loss in the aesthetic zone can be treated with both materials. DBBM presents a more favourable cost, while DBBM-C has unique handling properties that may benefit particular clinical situations and may fit the personal preferences of some practitioners.

Introduction

Numerous experimental studies and clinical trials demonstrated that, after tooth extraction, spontaneous healing will lead to loss of volume and shape of the extraction socket (Cardaropoli *et. al.*, 2003; Araujo & Lindhe, 2005; Hämmerle *et al.*, 2012; Araújo *et al.*, 2015). Consequently, the post-extraction alveolar dimensions are reduced both horizontally and vertically (Cardaropoli *et. al.*, 2012). Clinically, common findings associated with such bone remodelling processes are aesthetic problems and an increased need for bone grafting when dental implants are chosen for tooth replacement (Lekovic *et al.*, 1998).

Procedures for alveolar ridge preservation in non-molar areas have been proposed to decrease the frequency and severity of the clinical problems listed above (Jung *et al.*, 2013; Meloni *et al.*, 2015; Araújo *et al.*, 2015; Nart *et al.*, 2017).

Demineralized bovine bone mineral (DBBM) and demineralized bovine bone mineral mixed with 10% collagen (DBBM-C) are commonly used for alveolar ridge preservation (Jung *et al.*, 2013; Meloni *et al.*, 2015; Araújo *et al.*, 2015; Nart *et al.*, 2017). The placement of a collagen matrix (CM) to seal the socket entrance is a common procedure, presenting similar results compared with autogenous free gingival graft and a reduced patient morbidity (Jung *et al.*, 2013; Meloni *et al.*, 2015). However, there is scarce evidence comparing the same material, mixed or not with 10% collagen, sealed with a collagen matrix, in the anterior region (canines, laterals and central incisors). This question becomes even more interesting when the cost-benefit is analysed since the addition of collagen increases the cost of the material and, consequently the price charged for the procedure. The material handling is another clinically relevant question, as the materials properties differ. While DBBM-C

must be trimmed and adapted to the socket, DBBM has the conventional handling of a particulate biomaterial.

Thus, in light of these questions, the primary objective of this study was to test the non-inferiority of demineralized bovine bone mineral (DBBM) compared with demineralized bovine bone mineral with 10% collagen (DBBM-C), regarding the change in horizontal ridge width 1 mm below the buccal alveolar crest, after tooth extraction in the anterior maxilla.

Material and Methods

Study design

The present study was designed as a randomized, controlled, double-blind, parallel non-inferiority clinical trial. The bone substitutes were tested in post-extraction sockets of maxillary anterior teeth (canines, lateral and central incisors). All patients were treated at the Dental Clinic of Periodontology, University of São Paulo, São Paulo, Brazil. The study was approved by the Ethical Review Board (Dental School - University of São Paulo) on February 2016 (n° 1.664.774) and was conducted in accordance with the Helsinki Declaration of 1975 as revised in 2003. Informed consent was obtained from all patients prior to the start of the study. This study was registered at the Brazilian Clinical Trials Registry (ReBec: RBR-354q7d).

Patient population

Patients requiring extraction of one single maxillary anterior tooth (canines, lateral and central incisors) were recruited. The indications for tooth extractions were caries, endodontic complications (e.g., root fracture), periodontitis, and orthodontic

and prosthetic reasons. The patients had to fulfil the following inclusion and exclusion criteria:

Inclusion criteria

1. Age: > 18 years;
2. Need for tooth extraction in the anterior maxilla (13-23) due to caries, fractures, restorative problems, endodontic complications (e.g., instrument fracture) and orthodontic and prosthetic reasons;
3. Presence of one adjacent tooth at the extraction site;
4. Adequate oral hygiene (Bleeding on probing <20%; Plaque index <20%);
5. Patients classified as ASA I or II status (American Society of Anesthesiologists Classification);
6. Presence of at least 50% of the buccal bone plate;
7. Signed Informed Consent Form.

Exclusion criteria

1. Pregnant or lactating women;
2. Existence of bone metabolic disease;
3. Currently taking drugs that influence bone metabolism;
4. History of malignancy, radiotherapy or chemotherapy;
5. Tooth loss caused by severe periodontal disease;
6. Presence of acute periapical lesion;
7. Smokers (>10 cigarettes/day);
8. Artefacts that could affect the accuracy of CBCT measurements.

Randomization

The participants were screened by two investigators (A.H.L & V.M.S.). A random sequence was generated using software (Random Allocation 2.0, Informer Technologies Inc., USA), with random block sizes of 2 and 4 individuals. Allocation concealment was implemented with sequentially numbered opaque sealed envelopes. After extraction and socket cleaning, the envelope with the previously generated sequence was opened by a clinician not involved in the study, and the patient was randomly assigned to one of two groups:

1. DBBM-C group (reference treatment): demineralized bovine bone mineral with 10% collagen (DBBM-C; Bio-Oss® Collagen, Geistlich Pharma AG, Switzerland) + collagen matrix (CM; Mucograft Seal® Geistlich Pharma AG, Wolhusen, Switzerland) (n=33);
2. DBBM group: demineralized bovine bone mineral (DBBM; Bio-Oss®, Geistlich Pharma AG, Switzerland) + CM (n=33).

The patients and the examiner (V.M.S.) were blinded for the treatment group.

Treatment protocol and follow-up

A surgeon (A.H.L.) performed all of the procedures for both groups. The width of keratinized tissue was recorded with a periodontal probe, in all sites, from the centre of the buccal gingival margin to the mucogingival junction. The gingival phenotype was recorded according to Manjunath *et al.* (2015) by gingival transparency during probing. Flapless tooth extraction was performed exerting the least possible trauma to preserve soft and hard tissues, especially the buccal bone plate. After tooth extraction, the granulation tissue inside the socket was removed with hand instruments, and the alveolus was rinsed with saline solution. The heights

of the buccal and palatal bone plates were measured from the base of the socket using a periodontal probe to the nearest 0.5 mm, allowing the calculation of vertical loss of the buccal bone plate compared with the palatal wall (Jung *et al.* 2012). Subsequently, the soft tissue borders were de-epithelialized using a diamond drill under copious irrigation with saline solution.

The materials were gently placed and adapted within the experimental site up to the level or slightly above the bony envelope. Then, the top of the socket was covered with a CM positioned with six interrupted single sutures. The time to place and adapt DBBM and DBBM-C was recorded. A silicone impression was taken right after suturing. Radiographic examination was also performed immediately after the ridge preservation procedure using cone beam computed tomography (CBCT) (Carestream CS9300, Carestream, USA). The field of view (FOV) of a cylinder measuring 8x8 cm was selected, and an image was acquired with 0.16 mm of resolution. All patients received systemic antibiotics (amoxicillin 500 mg, t.i.d.) during the first week after surgery, and sutures were removed after 14 days. After 4 months, the patients were recalled for the second CBCT. Silicone impressions and standardized clinical photographs were also taken at 4 months.

Radiographic analysis and outcomes

Cone beam computed tomography (CBCT) was performed at baseline (BL: immediately after tooth extraction) and at 4 months (FU: before implant surgery). Open source software (3D Slicer 4.5, www.slicer.org) was used to process and superimpose the two time points in DICOM (Digital Imaging and Communications in Medicine) files. The areas where no changes had taken place during the follow-up periods (e.g., the cranial base and nasal septum) were used to match the datasets,

superimposing the baseline and 4-month follow-up datasets. Subsequently, the central region of the extraction socket was selected and exported at the same location in all obtained CBCT scans as image files. Image-editing software (Adobe Photoshop CS6, Adobe Systems, USA) was used to superimpose the exported images in layers. The following reference points and lines were set, according to the baseline image, as a new layer: the most apical point of the extraction socket; a vertical reference line, in the centre of the extraction socket (crossing the apical reference point); and horizontal reference lines, perpendicular to the vertical line at three different levels (at 1 mm, 3 mm and 5 mm below the margin of the palatal bone crest) (Fig. 1). The following measurements were then performed by a single and calibrated examiner (V.M.S.) and were repeated with a 2-week interval (ICC > 0.9) using image analysis software (ImageJ, ImageJ64, National Institute of Health, USA):

1. Thickness of the buccal bone plate at three levels (1 mm, 3 mm, and 5 mm below the most coronal point of the crest: BHP-1, BHP-3, BHP-5). If there was no buccal bone plate at the region of the reference line, the measurement was considered “zero”;
2. Horizontal ridge width measured at three levels (at -1 mm, -3 mm, -5 mm) below the most coronal point of the palatal crest (HW-1, HW-3, HW-5);
3. Height of the buccal (B) and palatal (P) bone plates from the apical end of the socket to the coronal level of the socket or ridge.

The primary outcome was change of the horizontal ridge width 1 mm below the buccal alveolar crest (HW-1), evaluated 4 months post-extraction. The following outcomes were secondary: BHP-1, BHP-3, BHP-5, HW-3, HW-5, and heights of the

buccal and palatal bone plates. A non-inferiority test was performed for the primary outcome only. All secondary outcomes tested the superiority of DBBM and DBBM-C.

Implant placement

All ridges presenting more than 4 mm horizontal ridge width were eligible for implant placement. If the horizontal ridge width measured less than 4 mm at 1 mm below the alveolar crest, primary bone augmentation was performed, and implants were placed at a later stage.

The placement of dental implants (Bone Level Tapered, Straumann AG, Switzerland) was performed 4 months after alveolar ridge preservation. All implant surgeries followed the same protocol, i.e., linear incision at the top of the ridge and full-thickness flap elevation. After incision and flap elevation, the implant beds were drilled, and implants were placed according to:

1. Optimal 3D position for a screw-retained reconstruction;
2. After implant placement, the sites presenting buccal dehiscence, fenestration or showing less than 1 mm of reminiscent bone around the implant were treated with guided bone regeneration (GBR) (Bio-Oss Small Granules associated with Bio-Gide, Geistlich AG, Switzerland);
3. All canines received regular diameter implants (BLT RC 4.1 mm, Straumann AG, Switzerland);
4. All lateral incisors received narrow diameter implants (BLT NC 3.3 mm, Straumann AG. Switzerland);
5. Central incisors received narrow implants (BLT NC 3.3 mm Straumann AG. Switzerland) in cases where diameter reduction allowed implant

placement and/or facilitated the procedure; e.g., avoiding or decreasing the complexity of an additional GBR.

After periosteal releasing incisions, tension-free adaptation of the wound margins was achieved with single interrupted sutures. The implants were left for submerged healing. All patients received systemic antibiotics (amoxicillin 500 mg, t.i.d.) and analgesics (paracetamol 750 mg, t.i.d.) during the first week after surgery. Sutures were removed after 14 days.

Sample size calculation

Sample size calculation was based on data from the Jung et al. (2013) study. The noninferiority margin was set at 0.5 mm for HW-1. Considering a standard deviation of 0.7 mm, a significance level of 2.5% and 80% statistical power, 31 subjects per group would be necessary. Considering possible losses to follow-up, 33 patients per group were included.

Statistical analysis

The reproducibility of measurements was assessed by an intraclass correlation coefficient (ICC) between two datasets performed at different time points by the same examiner.

Descriptive analysis was performed to assess means and standard deviations for each group. Significant differences between groups were calculated using the independent samples t-test. For the primary outcome variable (HW-1), confidence intervals of 95% (CI) were calculated. Non-inferiority of DBBM could be claimed if the lower limit of the CI (for the difference in mean change of HW-1) was below the non-inferiority margin (0.5 mm). The non-inferiority test was performed for the primary

variable only. The superiority of DBBM-C over DBBM was tested for all secondary outcomes using the independent samples t-test. The level of significance was set at 5%.

Results

Two hundred seventy-five patients were initially screened. Eighty-two patients received tooth extraction. Out of these 82 patients, 16 patients were not included due to the presence of defects >50% of the total height of the buccal plate. Sixty-six patients were randomized. One patient was lost during the follow-up period of 4 months due to personal reasons. Finally, 65 patients completed the study from March 2016 to June 2017. After tooth extraction, 32 patients were assigned to DBBM-C group and 33 patients to DBBM group (Fig. 2). After 4 months of socket healing, 64 patients received dental implants (BLT, Straumann AG, Switzerland), and one patient moved to another city before implant placement. No complications were recorded during either tooth extraction or implant placement. Thirty-two sockets presented intact buccal bone plates, 13 in the DBBM-C group and 19 in the DBBM group. Thirty-three sockets presented a small defect, with 19 in the DBBM-C group (1.42 mm±0.67 mm) and 14 in the DBBM group (1.5 mm±0.70 mm). No statistically significant differences were observed between the groups at baseline. The baseline demographic data, GBR procedure and implant diameters for each group are shown in Table 1. Sixty-five patients underwent CBCT analysis, 32 in group DBBM-C and 33 in group DBBM. The mean times to perform the ridge preservation procedure were 229 seconds (±52 seconds) for DBBM-C and 204 seconds (±63 seconds) for DBBM (p=0.98; -26 [95% CI -56;5). The mean thicknesses of the buccal bone plate at 1 mm, 3 mm and 5 mm measured 0.45 mm (±0.31 mm), 0.66 mm (±0.35 mm) and 0.68 mm (±0.33 mm) for the DBBM-C group and 0.54 mm (±0.25 mm), 0.67 mm

(±0.29 mm) and 0.66 mm (±0.23 mm) for the DBBM group, with no significant difference between the groups (p>0.05). The buccal and palatal heights were also assessed, showing 11.12 mm (±1.97 mm) for B and 11.29 mm (±2.40 mm) for P in the DBBM-C group and 10.54 mm (±2.64 mm) for B and 11.56 mm (±2.72 mm) for P in the DBBM group, with no significant difference between the groups (p>0.05) (Table 2).

The primary outcome (horizontal change at 1 mm - HW-1) was tested for non-inferiority between DBBM-C (reference treatment) and DBBM (test treatment). No statistically significant differences were detected when comparing the two experimental groups. The DBBM-C group showed a mean loss of -1.60 mm ±0.82 mm, while the DBBM group showed a mean loss of -1.37 mm ±0.84 mm (p=0.81, 0.23 [95% CI -0.19;0.64]). Therefore, the DBBM group demonstrated non-inferiority to the DBBM-C group (Fig. 3). Similar observations were made for HW-3 and HW-5. HW-3 showed -0.98 mm (±0.67 mm) for DBBM-C and -0.84 mm (±0.62 mm) for DBBM (p=0.40, 0.12 [95% CI -0.19; 0.45]). HW-5 showed - 0.67 mm (±0.47 mm) for DBBM-C and -0.56 mm (±0.48 mm) for DBBM (p=0.36, 0.11 [95% CI -0.13;0.34]). The details can be found in Table 3 and Fig. 4.

Discussion

The present study showed that, for maxillary anterior teeth, demineralized bovine bone mineral (DBBM) was non-inferior to demineralized bovine bone mineral with 10% collagen (DBBM-C) for the maintenance of bone volume 4 months after tooth extraction. This is the first RCT investigating the performance of an alveolar ridge preservation technique in a sample composed exclusively of maxillary anterior teeth in patients with aesthetic demands.

Both biomaterials tested, with and without 10% collagen, demonstrated a non-inferior difference of the primary outcome of 0.23 mm (95% CI -0.19 to 0.64) at HW-1. Within the predefined non-inferiority margin (0.5 mm), DBBM can be considered non-inferior to DBBM-C in maintaining the alveolar bone volume in defects with <50% of buccal bone loss. This outcome may be associated with the self-containing characteristics of the anterior defects in the present study, making the use of collagen to increase the agglutination and the stability of DBBM granules less critical. However, it can be hypothesized that a different outcome would be expected in defects with more than 50% buccal wall loss. The presence of collagen may be important in non-contained defects, providing the additional 3D stability necessary for bone formation. However, further studies will be necessary to test such an hypotheses.

Material handling is also an important question, and DBBM-C must be shaped according to the root anatomy to fill the socket. This step is technically simple, not time consuming, with a short learning curve, and some users consider DBBM-C easier to handle than granules. For vertical defects around teeth and implants or buccal defects around implants, it is evident that the addition of collagen favours the placement and the manipulation of the material. In addition, the collagen can avoid

particle dispersion during membrane placement, facilitating one of the key steps in regenerative procedures. This might be explained by the relatively simple type of extraction socket in the anterior maxilla and the easy accessibility in these areas of the jaws.

Despite the non-significant differences between the groups, the amount of loss at HW-1 was slightly lower in sites where DBBM was used, -17.53% vs. -21.12%, for DBBM and DBBM-C, respectively. Similar trends were also found at HW-3 and HW-5. In the anterior areas (maxillary canines, lateral and central incisors), both materials were unable to completely prevent vertical and horizontal loss during the healing phase. However, the amount of horizontal loss (-1.6 and -1.37 for DBBM-C and DBBM at 1 mm below the palatal crest, respectively) was considerably less when compared with results in sites of spontaneous healing (-3.6 mm reported by Barone *et al.*, 2012, and -3.3 mm by Jung *et al.*, 2013). Vertical changes showed minor bone remodelling on the palatal wall (approximately -10%), but greater resorption on the buccal wall (>50%), which could be associated with the buccal bone thickness, ranging between 0.45 ± 0.31 mm and 0.68 ± 0.33 mm for both groups.

Previous studies documented that the thickness of the buccal bone wall varies according to the site (Huynh-Ba *et al.*, 2010; Vera *et al.*, 2012; Zekry *et al.*, 2014; Wang *et al.*, 2014), presenting a thinner buccal bone wall (<1 mm) in the anterior maxilla. Furthermore, studies demonstrated that the buccal bone thickness influences the extent of shrinkage during the healing and remodelling phase after tooth extraction (Ferrus *et al.*, 2010; Leblebicioglu *et al.*, 2013; Spinato *et al.*, 2014). As the present sample showed a thin BHP for both groups (<0.68 mm) a high amount of resorption of the buccal bone wall was confirmed. However, due to the

similarity of treatment and the initial thickness of the buccal bone wall, no correlation was found between the buccal thickness and horizontal ridge width.

A previous RCT (Jung *et al.*, 2013), using the same CBCT evaluation and inclusion criteria for buccal defects, found a mean change in ridge width at 1 mm of -1.2 mm (-17.4%) after 6 months of healing for the group using DBBM-C covered with a CM. This HW change is slightly lower than in the present study (-1.6 and -1.37 for DBBM-C and DBBM, respectively). Such a difference may be associated with sample composition, with half of the sample consisting of pre-molars in both the mandible and the maxilla. Another RCT (Meloni *et al.*, 2015) compared DBBM covered with CM versus CT grafts at the maxilla. They showed a horizontal change (at 1 mm) of -0.67 mm for the CM group, which is lower than the change observed in the present study, using the same treatment modality. Some differences in the inclusion criteria may assist in the interpretation of these differences. First, 67% of the sample was composed of pre-molars; second, all fenestrations or dehiscence defects ≥3 mm on the CBCT scan were excluded and, finally, while the present sample included 32 and 33 patients per group, Meloni et al. (2015) had 15 patients per group. Such methodological differences may justify, at least partially, the higher horizontal change found in the present study.

To our knowledge, there is only one previous study that compared DBBM versus DBBM-C (Nart *et al.*, 2017). They revealed similar results on the level of HW at 1 mm with -0.91 mm for DBBM and -1.53 mm for DBBM-C compared with the present study, demonstrating HW at 1 mm of -1.37 mm and -1.60 mm, respectively. Despite these similarities, some important limitations may hamper a direct comparison between the two studies. While the present study used a flapless approach and sealed the socket with CM, Nart et al. (2017) used a full-thickness flap

in combination with a collagen membrane. The present study included exclusively maxillary anterior teeth and accepted dehiscence <50% of the total height of the buccal plate. Conversely, Nart et al. (2017) also included premolars and accepted both maxillary and mandibular teeth. Lastly, but perhaps most importantly, 65 individuals (32 and 33 per group) completed the follow-up period in the present investigation. In contrast, only 21 individuals (11 teeth per group) participated in the final evaluation in the study conducted by Nart et al. (2017), and no implant placement data were provided. Most of the studies with similar methodologies fell short on sample size and appeared to be underpowered compared with the present study.

One of the main objectives of alveolar ridge preservation is to allow implant placement after tooth extraction. According to a recent systematic review, implant placement feasibility following alveolar ridge preservation (Mardas *et al.*, 2015) ranged between 88.9% and 100%. The present study is in line with this review and showed a 100% implant placement feasibility after alveolar ridge preservation. However, there is a large heterogeneity when further augmentation is needed (Mardas *et al.*, 2015). The lack of data regarding the implant diameter could affect the need for further augmentation, especially in the anterior zone. In the present study, 10.8% of patients received a GBR procedure at implant placement due to a buccal fenestration (9% in the DBBM group and 12.5% in the DBBM-C group). However, a high number of narrow-diameter implants were placed in the present study (72.7% in the DBBM group and 84.4% in the DBBM-C group). Narrow-diameter implants obviously reduce the need for bone augmentation.

Regardless of these interesting findings, some limitations of the present study need to be addressed. First, the present study did not include a spontaneous healing control group. The decision to not include a negative control is based on the main question of the present investigation, i.e., whether the collagen in DBBM-C would have an influence on the final bone volume. Considering the vast number of previously published studies that already included and documented the alveolar ridge preservation concept, the greater number of patients per group was prioritized instead of including one additional arm for a negative control.

Based on the present findings, further controlled clinical studies are necessary to better elucidate the situations in which the addition of collagen may have an advantage in terms of graft and volume stability. Parameters such as surgical time, clinical outcome, aesthetics, bone volume and long-term stability should also be analysed in other types of defects and clinical situations to assist in the understanding of the ideal indications.

Conclusions

The present randomized controlled clinical trial demonstrated the non-inferiority of demineralized bovine bone mineral (DBBM) compared to demineralized bovine bone mineral with 10% collagen (DBBM-C) in the maintenance of alveolar bone volume in the anterior maxilla.

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Tables

Table 1. Demographic data

	DBBM-C	DBBM
Age (years), Mean ± SD	41.9 ± 11.9	43.3 ± 10.3
Male/Female	15/17	19/14
Non-Smoker/Smoker/Former Smoker	23/07/02	29/04/0
Thin Biotype/Thick Biotype	29/03	26/07
Width of Keratinized Tissue (mm)	6.62 ± 1.56	6.41 ± 1.29
Central Incisor/Lateral Incisor/Canine	16/13/03	20/10/03
GBR Procedure at Implant Placement	4	3
Narrow/Regular Implant Diameter	27/05	24/09

Table 2. Thickness of buccal bone plate (BHP) below the buccal bone crest, ridge width (HW) and palatal (P) and buccal (B) heights in the baseline CBCT scan

	DBBM-C (Mean ± SD in mm)	DBBM (Mean ± SD in mm)	Difference [95% CI] (mm)
BHP-1	0.45 ± 0.31	0.54 ± 0.25	0.10 [-0.04; 0.24]
BHP-3	0.66 ± 0.35	0.67 ± 0.29	0.01 [-0.15; 0.17]
BHP-5	0.68 ± 0.33	0.66 ± 0.23	-0.02 [-0.17; 0.12]
HW-1	7.42 ± 0.92	7.78 ± 1.23	0.36 [-0.18; 0.90]
HW-3	7.64 ± 1.02	7.95 ± 1.51	0.31 [-0.33; 0.95]
HW-5	7.61 ± 1.17	7.94 ± 1.67	0.34 [-0.38; 1.06]
B	11.29 ± 2.40	11.56 ± 2.72	0.27 [-1.00; 1.55]
P	11.12 ± 1.97	10.54 ± 2.64	-0.58 [-1.74; 0.58]

Table 3. CBCT analysis of ridge height and width changes between baseline and 4 months follow-up in mm with 95% confidence intervals of the differences and percentage changes

	DBBM-C (Mean ± SD in mm)	DBBM (Mean ± SD in mm)	Difference [95% CI] (mm)
HW-1	-1.60 ± 0.82	-1.37 ± 0.84	0.23 [-0.19; 0.64]
HW-3	-0.98 ± 0.67	-0.84 ± 0.62	0.13 [-0.19; 0.45]
HW-5	-0.67 ± 0.47	-0.56 ± 0.48	0.11 [-0.13; 0.34]
B	-6.11 ± 3.71	-6.95 ± 3.82	-0.93 [-2.70; 1.04]
P	-1.13 ± 0.88	-1.03 ± 0.95	0.10 [-0.35; 0.56]
	DBBM-C (%)	DBBM (%)	
HW-1	-21.12 ± 9.64	-17.53 ± 10.04	
HW-3	-12.41 ± 7.90	-9.70 ± 8.34	
HW-5	-8.50 ± 5.71	-6.73 ± 5.35	
B	-53.23 ± 29.15	-59.44 ± 28.27	
P	-10.45 ± 8.29	-10.38 ± 10.58	

Figure Legends

Fig. 1. Cone-beam computed tomography (CBCT) slice section representing the most apical point of the extraction socket (yellow dot); a vertical reference line in the centre of the extraction socket crossing the apical reference point; horizontal reference lines perpendicular to the vertical line at 1 mm, 3 mm and 5 mm below the margin of the palatal bone crest.

Fig. 2. Flowchart of participant enrolment.

Fig. 3. Confidence intervals and the non-inferiority margin (0.5 mm). DBBM is non-inferior to DBBM-C but was not shown to be superior, as the confidence interval lies to the left of and includes zero.

Fig. 4. Cone-beam computed tomography (CBCT) measurements: (a) Changes in ridge width (%) over 4 months (measured at three levels (at -1 mm, -3 mm, -5 mm) below the most coronal point of the palatal crest (HW-1, HW-3, HW-5); (b) Changes in ridge height (%) over 4 months for the buccal (B) and palatal (P) bone plates from the apical end of the socket to the coronal level of the socket or ridge.